

**IN THE CLAIMS:**

Kindly amend the claims as follows:

1                   1.     (Currently Amended)     A method of detecting a  
2 malignant tumor in a human subject, comprising:

3                   (a)     collecting a sample of a bodily substance containing human  
4                   nucleic acid or protein, said nucleic acid or protein having  
5                   originated from cells of the human subject;

6                   (b)     detecting quantitatively or semi-quantitatively in the sample  
7                   a level of expression for laminin  $\alpha$ 4 subunit protein or  
8                   laminin  $\alpha$ 4-specific mRNA; and

9                   (c)     comparing the expression level in (b) to a level of  
10                  expression in a normal control, wherein overexpression of  
11                  laminin  $\alpha$ 4 subunit protein or laminin  $\alpha$ 4-specific mRNA,  
12                  with respect to the control, indicates the presence of a  
13                  malignant tumor in the human subject.

1                   2.     (Previously Presented)     The method of Claim 1, wherein  
2 the bodily substance is blood, urine, lymph, cerebro-spinal fluid, skin, stroma,  
3 vascular epithelium, oral epithelium, vaginal epithelium, cervical epithelium,  
4 uterine epithelium, intestinal epithelium, bronchial epithelium, esophageal  
5 epithelium, or mesothelium.

1                   3.     (Previously Presented)     The method of Claim 1, wherein  
2 the bodily substance is a tissue sample.

1                   4.     (Original)     The method of Claim 3, wherein the tissue  
2     sample is collected from the brain of the subject.

1                   5.     (Original)     The method of Claim 3, wherein the tissue  
2     sample is a tumor tissue.

1                   6.     (Original)     The method of Claim 1, wherein the bodily  
2     substance is plasma.

1                   7.     (Original)     The method of Claim 1, wherein the bodily  
2     substance is a cellular material.

1                   8.     (Original)     The method of Claim 7, wherein the cellular  
2     material is derived from the human subject's brain kidney, bladder, ureter,  
3     urethra, thyroid, parotid gland, submaxillary gland, sublingual gland, lymph  
4     node, bone, cartilage, lung, mediastinum, breast, uterus, ovary, testis,  
5     prostate, cervix uteri, endometrium, pancreas, liver, spleen, adrenal,  
6     esophagus, stomach, or intestine.

1                   9.     (Previously Presented)     The method of Claim 7, wherein  
2     the cellular material is a carcinoma, sarcoma, lymphoma, mesothelioma,  
3     melanoma, glioma, nephroblastoma, glioblastoma, oligodendroglioma,  
4     astrocytoma, ependymoma, primitive neuroectodermal tumor, atypical  
5     meningioma, malignant meningioma, or neuroblastoma.

1                   10.   (Previously Presented)   The method of Claim 8, wherein  
2   the cellular material is a hyperplastic and/or cytologically dysplastic cellular  
3   growth or proliferation that is benign prostatic hyperplasia/dysplasia or cervical  
4   hyperplasia/dysplasia.

11-12 (Cancelled)

1                   13.   (Previously Presented)   The method of Claim 2, wherein  
2   the expression level of laminin  $\alpha$ 4-specific mRNA is detected by measuring  
3   RNA.

1                   14.   (Previously Presented)   The method of Claim 2, wherein  
2   the expression level of laminin 4-specific mRNA is detected by measuring  
3   cDNA.

1                   15.   (Previously Presented)   The method of Claim 2, wherein  
2   a gene expression microarray is used to detect the level of expression of  
3   laminin  $\alpha$ 4-specific mRNA.

1                   16.   (Previously Presented)   The method of Claim 1, further  
2   comprising detecting the overexpression of laminin  $\beta$ 1 subunit protein or  
3   *laminin*  $\beta$ 1-specific mRNA relative to the normal control.

1           17. (Original Claim) The method of Claim 1, further  
2 comprising detecting quantitatively or semi-quantitatively in the sample a level  
3 of expression with respect to a normal control, of a gene encoding a protein  
4 selected from the group consisting of insulin-like growth factor binding protein  
5 precursor 3, transforming growth factor- $\beta$ -induced gene, vascular endothelial  
6 growth factor, connective tissue growth factor, human insulin-like growth  
7 factor binding protein precursor 5, placental growth factor, transcription factor  
8 Ap-2, human insulin-like growth factor II, epidermal growth factor receptor,  
9 matrix metalloproteinase-2, keratin 18, vimentin, fibronectin 1, phospholipase  
10 A2 receptor, desmoplakin, tropomodulin, tenascin C, and collagen type IV  $\alpha$ 1  
11 chain, or detecting a combination of expression levels for any of these.

1           18. (Currently Amended) A method of diagnosing the  
2 presence of a glioma in a human subject, comprising:

- 3           (a) obtaining a sample from the brain of the human subject;  
4           (b) detecting quantitatively or semi-quantitatively in the sample  
5 a level of expression for laminin  $\alpha$ 4 subunit protein or  
6 *laminin  $\alpha$ 4*-specific mRNA; and  
7           (c) comparing the expression level in (b) to a level of  
8 expression in a normal control, wherein overexpression of  
9 laminin  $\alpha$ 4 subunit protein or *laminin  $\alpha$ 4*-specific mRNA,  
10 with respect to the control, indicates the presence of  
11 glioma in the subject.

19-20 (Cancelled).

1                   21.   (Previously Presented)   The method of Claim 18, wherein  
2 the expression level of *laminin*  $\alpha 4$ -specific mRNA is detected by measuring  
3 RNA.

1                   22.   (Previously Presented)   The method of Claim 18, wherein  
2 the expression level of *laminin*  $\alpha 4$ -specific mRNA is detected by measuring  
3 cDNA.

1                   23.   (Previously Presented)   The method of Claim 18 wherein  
2 a gene expression microarray is used to detect the level of expression of  
3 *laminin*  $\alpha 4$ -specific mRNA.

1                   24.   (Currently Amended)   The method of Claim 18, further  
2 comprising detecting the overexpression of *laminin*  $\beta 1$  subunit protein or  
3 *laminin*  $\beta 1$ -specific mRNA relative to the normal control.

1                   25.   (Original Claim)   The method of Claim 18, further  
2 comprising detecting quantitatively or semi-quantitatively in the sample a level  
3 of expression with respect to a normal control, of a gene encoding a protein  
4 selected from the group consisting of insulin-like growth factor binding protein  
5 precursor 3, transforming growth factor- $\beta$ -induced gene, vascular endothelial  
6 growth factor, connective tissue growth factor, human insulin-like growth  
7 factor binding protein precursor 5, placental growth factor, transcription factor  
8 Ap-2, human insulin-like growth factor II, epidermal growth factor receptor,  
9 matrix metalloproteinase-2, keratin 18, vimentin, fibronectin 1, phospholipase  
10 A2 receptor, desmoplakin, tropomodulin, tenascin C, and collagen type IV  $\alpha 1$   
11 chain, or detecting a combination of expression levels for any of these.

1                   26. (Original Claim)     The method of Claim 18, wherein the  
2     sample is a tumor tissue.

1                   27. (Original Claim)     The method of Claim 18, wherein the  
2     sample comprises plasma.

1                   28. (Currently Amended)     A method of predicting the  
2     recurrence of a malignant tumor in a human subject from whom a tumor has  
3     been resected, comprising:

4                   (a) obtaining a tissue sample from the human subject, said tissue  
5                   sample being from a region adjacent to the site of the  
6                   tumor;

7                   (b) detecting quantitatively or semi-quantitatively a level of  
8                   expression for laminin  $\alpha$ 4 subunit protein or laminin  $\alpha$ 4-  
9                   specific mRNA in the sample; and

10                  (c) comparing the expression level in (b) to a level of expression  
11                  in a normal tissue control, wherein overexpression of  
12                  laminin  $\alpha$ 4 subunit protein or laminin  $\alpha$ 4-specific mRNA,  
13                  with respect to the control, is predictive of a recurrence of  
14                  a malignant tumor in the subject.

1                   29. (Original Claim)     The method of Claim 28, wherein the  
2     tissue sample is histopathologically normal in appearance.

30 -31 (Cancelled).

1                   32.   (Previously Presented)   The method of Claim 28, wherein  
2   the expression level of laminin  $\alpha$ 4-specific mRNA is detected by measuring  
3   RNA.

1                   33.   (Previously Presented)   The method of Claim 28, wherein  
2   the expression level of laminin  $\alpha$ 4-specific mRNA is detected by measuring  
3   cDNA.

1                   34.   (Previously Presented)   The method of Claim 28, wherein  
2   a gene expression microarray is used to detect the level of expression of  
3   *laminin  $\alpha$ 4*-specific mRNA.

1                   35.   (Original Claim)   The method of Claim 28, further  
2   comprising detecting quantitatively or semi-quantitatively in the sample a level  
3   of expression with respect to a normal tissue control, of a gene encoding a  
4   protein selected from the group consisting of insulin-like growth factor binding  
5   protein precursor 3, transforming growth factor- $\beta$ -induced gene, vascular  
6   endothelial growth factor, connective tissue growth factor, human insulin-like  
7   growth factor binding protein precursor 5, placental growth factor,  
8   transcription factor Ap-2, human insulin-like growth factor II, epidermal growth  
9   factor receptor, matrix metalloproteinase-2, keratin 18, vimentin, fibronectin  
10   1, phospholipase A2 receptor, desmoplakin, tropomodulin, tenascin C, and  
11   collagen type IV  $\alpha$ 1 chain, or detecting a combination of expression levels for  
12   any of these.

1                   36.   (Currently Amended)    The method of Claim 28, further  
2   comprising detecting the overexpression of laminin  $\beta$ 1 subunit protein or  
3   *laminin  $\beta$ 1*-specific mRNA relative to the normal tissue control.

37-43 (Cancelled).

1                   44.   (Currently Amended)    A method of predicting the  
2   recurrence of a glioma in a human subject from whom a glioma has been  
3   resected, comprising:

4                   (a)   obtaining a tissue sample from the brain of the human  
5                   subject, said tissue sample being from a region adjacent to  
6                   the site of the glioma;

7                   (b)   detecting quantitatively or semi-quantitatively a level of  
8                   expression for laminin  $\alpha$ 4 subunit protein or *laminin  $\alpha$ 4*-  
9                   specific mRNA in the sample; and

10                  (c) comparing the expression level in (b) to a level of expression  
11                  in a normal tissue control, wherein overexpression of  
12                  laminin  $\alpha$ 4 subunit protein or *laminin  $\alpha$ 4*-specific mRNA,  
13                  with respect to the control, is predictive of a recurrence of  
14                  glioma in the subject.

1                   45.   (Original Claim)    The method of Claim 44, wherein the  
2   tissue sample is histopathologically normal in appearance.

46-47 (Cancelled).



1                   48.   (Previously Presented)   The method of Claim 44, wherein  
2   the expression level of *laminin*  $\alpha$ 4-specific mRNA is detected by measuring  
3   RNA.

1                   49.   (Previously Presented)   The method of Claim 44, wherein  
2   the expression level of *laminin*  $\alpha$ 4-specific mRNA is detected by measuring  
3   cDNA.

1                   50.   (Previously Presented)   The method of Claim 44, wherein  
2   a gene expression microarray is used to detect the level of expression of  
3   *laminin*  $\alpha$ 4-specific mRNA.

1                   51.   (Original Claim)   The method of Claim 44, further  
2   comprising detecting quantitatively or semi-quantitatively in the sample a level  
3   of expression with respect to a normal tissue control, of a gene encoding a  
4   protein selected from the group consisting of insulin-like growth factor binding  
5   protein precursor 3, transforming growth factor- $\beta$ -induced gene, vascular  
6   endothelial growth factor, connective tissue growth factor, human insulin-like  
7   growth factor binding protein precursor 5, placental growth factor,  
8   transcription factor Ap-2, human insulin-like growth factor II, epidermal growth  
9   factor receptor, matrix metalloproteinase-2, keratin 18, vimentin, fibronectin  
10   1, phospholipase A2 receptor, desmoplakin, tropomodulin, tenascin C, and  
11   collagen type IV  $\alpha$ 1 chain, or detecting a combination of expression levels for  
12   any of these.

1                   60. (Currently Amended)     A method of ~~establishing a grade~~  
2 ~~of ranking~~ a malignant tumor in a human subject, wherein said ~~grade ranks~~  
3 ranking orders the tumors in terms of invasiveness and ~~agressiveness~~  
4 aggressiveness, comprising:

5                   (a) obtaining a tissue sample from the human subject, said  
6 sample comprising a cell expressing a plurality of mRNA  
7 species that are detectably distinct from one another;

8                   (b) detecting quantitatively or semi-quantitatively an  
9 expression level for at least two of the plurality of mRNA  
10 species, wherein at least one of the detected mRNA  
11 species is a *laminin*  $\alpha 4$ -specific mRNA and at least one is  
12 specific to a growth factor-related gene or to a structural  
13 gene other than a laminin gene;

14                  (c) constructing an expression profile of the sample comprising  
15 a combination of the detected expression levels of *laminin*  
16  $\alpha 4$ -specific mRNA and the at least one other mRNA species  
17 specific to the growth factor-related gene or to the  
18 structural gene other than a laminin gene; and

19                  (d) comparing the expression profile in (c) to an expression  
20 profile for a normal tissue control, wherein a level of  
21 overexpression of *laminin*  $\alpha 4$ -specific mRNA, with respect  
22 to the control, is indicative of the presence of and degree  
23 of invasiveness of the tumor in the subject, wherein a level  
24 of overexpression of the structural gene other than a  
25 laminin gene, with respect to the control, is indicative of  
26 degree of tumor invasiveness, and wherein a level of  
27 overexpression of the growth factor-related gene, with

1                   56. (Original Claim) The method of Claim 54, wherein the  
2 expression level of *laminin*  $\alpha 4$ -specific mRNA is detected by measuring cDNA.

1                   57. (Original Claim) The method of Claim 53, further  
2 comprising detecting quantitatively or semi-quantitatively in the sample a level  
3 of expression with respect to a normal tissue control, of a growth factor-  
4 related gene encoding a protein selected from the group consisting of insulin-  
5 like growth factor binding protein precursor 3, transforming growth factor- $\beta$ -  
6 induced gene, vascular endothelial growth factor, connective tissue growth  
7 factor, human insulin-like growth factor binding protein precursor 5, placental  
8 growth factor, transcription factor Ap-2, human insulin-like growth factor II,  
9 and epidermal growth factor receptor, whereby the relative aggressiveness of  
10 the glioma is predicted.

1                   58. (Original Claim) The method of Claim 53, further  
2 comprising detecting quantitatively or semi-quantitatively in the sample a level  
3 of expression with respect to a normal tissue control, of a structural gene  
4 encoding a protein selected from the group consisting of matrix  
5 metalloproteinase-2, keratin 18, vimentin, fibronectin 1, phospholipase A2  
6 receptor, desmoplakin, tropomodulin, tenascin C, and collagen type IV  $\alpha 1$   
7 chain, whereby the relative invasiveness of the glioma is predicted.

1                   59. (Original Claim) The method of Claim 53, further  
2 comprising detecting the overexpression of *laminin*  $\beta 1$ -specific mRNA relative  
3 to the normal tissue control.

1           52. (Currently Amended)    The method of Claim 44, further  
2 comprising detecting the overexpression of laminin  $\beta$ 1 subunit protein or  
3 *laminin  $\beta$ 1*-specific mRNA relative to the normal tissue control.

1           53. (Original Claim)    A method of predicting recurrence of a  
2 glioma in a human subject from whom a glioma has been resected,  
3 comprising:

4           (a) obtaining a tissue sample from the brain of a human  
5 subject, said tissue sample being from a region adjacent to  
6 the site of the glioma, said sample comprising a cell  
7 expressing a plurality of mRNA species that are detectably  
8 distinct from one another;

9           (b) detecting quantitatively or semi-quantitatively an  
10 expression level for *laminin  $\alpha$ 4*-specific mRNA; and

11          (c) comparing the expression level in (b) to a level of expression  
12 in a normal tissue control, wherein overexpression of  
13 *laminin  $\alpha$ 4*-specific mRNA, with respect to the control, is  
14 predictive of a recurrence of glioma in the subject.

1           54. (Original Claim)    The method of Claim 53, wherein a  
2 gene expression microarray is used to detect the level of expression of *laminin*  
3  *$\alpha$ 4*-specific mRNA.

1           55. (Original Claim)    The method of Claim 54, wherein the  
2 expression level of *laminin  $\alpha$ 4*-specific mRNA is detected by measuring RNA.

28                    respect to the control, is indicative of degree of tumor  
29                    aggressiveness.  
30

1                    61. (Original Claim) The method of Claim 60, wherein the  
2 growth factor-related gene encodes a protein selected from the group  
3 consisting of insulin-like growth factor binding protein precursor 3,  
4 transforming growth factor- $\beta$ -induced gene, vascular endothelial growth factor,  
5 connective tissue growth factor, human insulin-like growth factor binding  
6 protein precursor 5, placental growth factor, transcription factor Ap-2, human  
7 insulin-like growth factor II, and epidermal growth factor receptor.

1                    62. (Original Claim) The method of Claim 60, wherein the  
2 structural gene encodes a protein selected from the group consisting of matrix  
3 metalloproteinase-2, keratin 18, vimentin, fibronectin 1, phospholipase A2  
4 receptor, desmoplakin, tropomodulin, tenascin C, and collagen type IV  $\alpha$ 1  
5 chain.

1                    63. (Original Claim) The method of Claim 60, wherein the  
2 expression level of *laminin*  $\alpha$ 4-specific mRNA is detected by measuring RNA.

1                    64. (Original Claim) The method of Claim 60, wherein the  
2 expression level of *laminin*  $\alpha$ 4-specific mRNA is detected by measuring cDNA.

1                    65. (Original Claim) The method of Claim 60, wherein a  
2 gene expression microarray is used to detect the level of expression of *laminin*  
3  $\alpha$ 4-specific mRNA.

1                   66. (Original Claim)    The method of Claim 60, further  
2 comprising detecting the overexpression of *laminin*  $\beta$ 1-specific mRNA relative  
3 to the normal tissue control.

1                   67. (Original Claim)    The method of Claim 60, wherein the  
2 tissue sample is brain tissue.

1                   68. (Original Claim)    The method of Claim 60, wherein the  
2 tumor is a glial tumor.

69-74 (Cancelled).

1                   75. (Previously Presented)   The new method of Claim 1,  
2 further comprising detecting the overexpression of a gene encoding laminin  $\beta$ 1  
3 subunit relative to the normal control.

1                   76. (Previously Presented)   The method of Claim 18, further  
2 comprising detecting the overexpression of a gene encoding laminin  $\beta$ 1 subunit  
3 relative to the normal control.

1                   77. (Previously Presented)   The method of Claim 28, further  
2 comprising detecting the overexpression of a gene encoding laminin  $\beta$ 1 subunit  
3 relative to the normal control.

1                   78. (Previously Presented)   The method of Claim 44, further  
2 comprising detecting the overexpression of a gene encoding laminin  $\beta$ 1 subunit  
3 relative to the normal control.